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Pulmonary involvement in connective tissue diseases.

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SUMMARY AND CONCLUSIONS

Connective tissue diseases (CTD) are characterized by disease manifestations in several organs and the presence of circulating autoantibodies to non-organ-specific antigens, in particular nuclear antigens. Although the pathogenesis of CTD is as yet only partially elucidated, immunologically mediated damage of the microvasculature is commonly suggested to be one of the major mechanisms. This theory is supported by the high prevalence of Raynaud's phenomenon and the presence of morphological abnormalities of the capillaries in kidney, skin, nailfold and lung tissue of patients with systemic lupus erythematosus (SLE) and scleroderma. In addition, perivascular mononuclear infiltrates have been demonstrated in lung tissue specimens of patients with scleroderma, suggesting that microvascular damage may also play a role in pulmonary involvement in connective tissue diseases. However, this has not been firmly established. In SLE, pathological studies have not shown consistent results. Pulmonary immune complex depositions have been found but could not be confirmed in other studies. Given the similarities between the clinical course of interstitial lung involvement in SLE and scleroderma, the fact that a scleroderma-like connective tissue disease pattern, including interstitial lung disease, can occur in chronic graft versus host disease may suggest that pulmonary involvement is an immunological process with a pivotal role for the T-lymphocyte in both scleroderma and SLE. This would be compatible with the fact that lymphocyte alveolitis, as reflected by a high number of lymphocytes in the bronchoalveolar lavage (BAL) fluid, is a common abnormality in patients with scleroderma and SLE.

In this thesis, interstitial pulmonary involvement in patients with CTD was studied in order to elaborate the hypothesis that immunologically mediated microvascular damage is the main pathophysiologic mechanism. Sensitive lung function testing, specifically assessment of the pulmonary diffusing capacity ($T_{l,CO}$) and its components D_m and V_c , and bronchoalveolar lavage were utilized to assess pulmonary involvement. Morphological evidence of microvascular damage was assessed by nailfold capillary microscopy. As a reference for the studies of BAL in scleroderma and SLE, a study of two relatively common varieties of ILD, representing both ends of the spectrum of lymphocyte and neutrophil alveolitis, i.e. sarcoidosis and idiopathic pulmonary fibrosis (IPF), respectively, is incorporated in this thesis.

In the first part of this thesis three studies of patients with various forms of CTD or in various stages of the development of CTD are described.

Chapter 1 describes the results of a prospective, longitudinal study with a follow-up of 6 years in a group of patients with RP, both with and without an underlying CTD. We found that pulmonary function abnormality is a rare finding in patients with RP without a diagnosis of an underlying CTD. Patients with serologic immunological abnormalities, however, had lower values of pulmonary function than patients without a positive test for autoantibodies, especially with

respect to $T_{l,CO}$. We concluded that pulmonary function testing in every patient presenting with RP without an underlying CTD does not appear clinically justifiable, in view of the low prevalence of pulmonary function abnormalities in these patients and the absence of deterioration of pulmonary function. Only patients who exhibit immunological abnormalities, i.e. autoantibodies, may be selected for pulmonary function testing and follow-up, since they are probably the ones at risk for developing a CTD with pulmonary involvement.

In **Chapter 2** we investigated whether functional evidence of pulmonary vascular damage is associated with extrapulmonary morphological vascular abnormalities observed at the nailfold capillaries. In a study population consisting of patients with RP at various stages in the disease spectrum from primary RP to RP with a fullblown CTD, we found that V_c , the component of $T_{l,CO}$ representing the pulmonary capillary blood volume, was below normal in 41 percent of patients with primary RP and undifferentiated CTD (vs 53 % in scleroderma). D_m , representing the diffusing capacity of the alveolocapillary membrane and related to structural changes in the membrane, was below normal in only 5 % and 26 % of patients with primary RP and undifferentiated CTD, respectively. In patients with Scleroderma or the CREST syndrome D_m was significantly decreased as compared to the former groups. D_m was also the pulmonary function parameter which correlated with both nailfold capillary abnormalities and the presence of antinuclear antibodies. These data led us to conclude that early pulmonary involvement in scleroderma-syndromes is functionally characterized by a lowered D_m , correlating with morphological changes of the nailfold capillaries. Decreased V_c may probably reflect Raynaud's phenomenon of the pulmonary vasculature.

Chapter 3 describes a similar study in a large group of patients with SLE, hypothesizing that patients with SLE and ILD represent an overlap of SLE and scleroderma and that microvascular damage is involved in the pathophysiology of ILD in both diseases. Indeed, we found that isolated impairment of $T_{l,CO}$ was associated with interstitial changes on chest X-ray and that the presence of scleroderma changes of the hands was associated with a restrictive lung function pattern. Nailfold capillary abnormalities correlated with decreased $T_{l,CO}$ and D_m , the component of $T_{l,CO}$ representing the diffusing capacity of the alveolocapillary membrane. Antibodies to U1-RNA were associated with restrictive lung function and decreased $T_{l,CO}$. We concluded that interstitial lung disease is present in a subset of SLE patients characterized by an increased prevalence of scleroderma traits and anti-(U1)RNA antibodies. Our data also suggested that microvascular changes contribute to the development of interstitial lung disease in SLE as well as in scleroderma.

In **chapter 4** a case report of a patient with SLE and pulmonary hypertension illustrates that an inflammatory component may also contribute to an increase in pulmonary vascular resistance leading to pulmonary hypertension. In the patient we describe, treatment with intermittent infusions of cyclophosphamide resulted

in marked clinical improvement as documented in summary stages in the course. Further decreased $T_{l,CO}$ changes of the scleroderma immunologic patients with does not warrant in particular development

In the second characteristic scleroderma, D-penicillamine representing IPF and lymph the diagnostic lymphocyte p **Chapter 5** discusses clinical and Sarcoidosis. alveolar macrophages normal lymphocyte O_2 production ratios in BAL in sarcoidosis. correlated in absolute number (respectively) ($r = -0.43$, and In patients with relationships were capacity ($r =$ Summarizing among patients production is that different sarcoidosis a disease duration progression.

in marked clinical improvement and partial improvement of pulmonary hypertension as documented by repeated hemodynamic evaluations.

In summary, our data show that ILD is increasingly prevalent in successive stages in the development of a CTD and that it follows a slowly progressive course. Functional parameters of pulmonary microvascular damage, i.e. decreased $T_{l,CO}$ and D_m , were associated with the presence of morphological changes of the nailfold capillaries and with the presence of autoantibodies in both scleroderma and SLE. These findings are compatible with a major role for immunologically mediated microvascular damage in the pathogenesis of ILD in patients with a connective tissue disease. The presence of Raynaud's phenomenon does not warrant routine lung function testing, although follow-up is indicated, in particular in patients with antinuclear antibodies, in view of the possible development of a CTD.

In the second part of this thesis we present two studies on the cellular characteristics of the inflammatory process in the lungs of patients with SLE and scleroderma, as well as the possibility of therapeutic intervention with D-penicillamine in the latter, introduced by a study in two other types of ILD, representing both ends of the spectrum of alveolitis, i.e. neutrophil alveolitis in IPF and lymphocyte alveolitis in sarcoidosis. In addition a case report illustrates the diagnostic use of BAL with determination of cell differentiation and lymphocyte phenotypes in patients with multiple ILD-associated diseases.

Chapter 5 describes a study on the relationship between BAL-derived and clinical and lung function parameters of ILD in patients with IPF and Sarcoidosis. Lymphocyte alveolitis in sarcoidosis was associated with increased alveolar macrophage (AM) O_2 production as compared to sarcoidosis with normal lymphocyte counts. Levels of serum ACE correlated positively with AM O_2 production. Patients with extrapulmonary sarcoidosis had higher CD4/CD8 ratios in BAL and shorter disease duration than those with strictly pulmonary sarcoidosis. Disease duration in sarcoidosis was shorter than in IPF and correlated inversely with the number of BAL cells ($r=-0.38$), the relative and absolute number of lymphocytes in BAL fluid ($r=-0.34$ and $r=-0.44$, respectively) and the percentage of CD4-positive cells and the CD4/CD8 ratio ($r=-0.43$, and $r=-0.48$, respectively).

In patients with sarcoidosis, but not in those with IPF, significant inverse relationships were observed between O_2 production of BAL cells and total lung capacity ($r=-0.67$) and the pulmonary diffusing capacity $T_{l,CO}$ ($r=-0.50$). Summarizing, our findings showed that lung lymphocyte phenotypes differ among patients with pulmonary and extrapulmonary sarcoidosis and that O_2 production is upregulated in active sarcoidosis. In addition, our findings suggest that different relationships between BAL data and lung function in patients with sarcoidosis and IPF may be explained by differences in disease duration. In IPF, disease duration is likely to be underestimated because of its insidious onset and progression. In sarcoidosis, the acute presence of extrapulmonary symptoms,

helpful to establish an early diagnosis, is associated with significant BAL lymphocytosis and lung function impairment.

In **chapter 6** we examined the relationship between peripheral blood and bronchoalveolar lavage lymphocyte phenotypes and lung function in 19 consecutive patients with SLE. In addition, the relationships between disease activity and lung function and lymphocyte phenotypes was evaluated. $T_{l,CO}$, K_{CO} and D_m correlated inversely with the numbers of CD8 positive cells and CD56/CD11 positive (NK-)cells in BAL. Oxygen radical production, both by stimulated and unstimulated BAL cells and blood PMNs was significantly increased in SLE. In comparison with healthy controls, patients with SLE had a lower percentage of CD19 positive cells in the BAL versus an increased percentage of these cells in peripheral blood. HLA-Dr expression on CD4 and CD8 positive lung lymphocytes was markedly increased in SLE. Current SLE disease activity was not associated with changes in lung or blood lymphocyte phenotypes or lung function. In conclusion, our data support the hypothesis of an important role for the T-lymphocyte in the development of ILD in SLE. No evidence for local B-cell proliferation was found. Our data do suggest that an ongoing cell-mediated immune response, particularly involving CD56/CD11 positive NK-cells and associated with upregulated local production of oxygen radicals and with impaired pulmonary diffusing capacity is present in the lungs in SLE and that this process seems to be independent from general SLE disease activity.

Chapter 7 describes the results of a pilot study on the therapeutic intervention with D-penicillamine in ILD in patients with scleroderma, conducted in a double blind, placebo-controlled crossover fashion. We found significant effects of D-penicillamine on BAL parameters. BAL lymphocytes and eosinophils decreased, both in relative and absolute numbers. Lung function assessments showed an increase in residual volume relative to total lung capacity (TLC) during treatment (1.9% without D-penicillamine vs 8.8% with D-penicillamine). We also observed beneficial systemic effects of D-penicillamine, i.e. a decrease of HLA-Dr expression on peripheral blood lymphocytes and a decrease of oxygen radical production by peripheral blood polymorphonuclear cells. We concluded that, in this pilot study, D-penicillamine has beneficial effects on lung inflammation, which may implicate a long-term favourable effect on the course of interstitial lung disease in scleroderma. The favourable results ask for confirmation by a multi-centre study with a longer follow-up period.

The case report described in **chapter 8** presents an intriguing coincidence of scleroderma, sarcoidosis and myositis, and illustrates the diagnostic use of bronchoalveolar lavage with determination of cell differentiation and lymphocyte phenotypes in patients with multiple ILD-associated diseases.

Taken together, the results of the studies in the second part of this thesis show that BAL is a valuable diagnostic and investigational tool in ILD. Although experience upto now has led to a certain discriminating power, the results of BAL should always be interpreted in the light of other parameters such as disease

duration, lung function, performed with BAL. The relationship between these parameters, suggest that NK-cells may play a role in the pathogenesis of ILD. In addition, the results of this pilot-study suggest that lung inflammation is a genuine possible cause of mor-

Overall, the results of this study suggest that immunopathophysiology is involved in the pathogenesis of ILD. In addition, ongoing alveolar damage is present in ILD, involving NK-cells and at least in scleroderma.

duration, lung function and the clinical status of the patient. Follow-up should be performed whenever possible in order to gain insight into the relationships between changes in lung inflammation with progression of the disease and other parameters, such as lung function. Our results of BAL in patients with SLE suggest that an ongoing cell-mediated immune response, particularly involving NK-cells may underly the development of ILD in this disease. The results of our pilot-study with D-penicillamine in patients with scleroderma lung disease show that lung inflammation can be influenced by this drug, and raise hopes for a genuine possibility for therapeutic intervention in this increasingly important cause of mortality in scleroderma.

Overall, the results of the studies presented in this thesis support the hypothesis that immunologically mediated microvascular damage is an important pathophysiological mechanism in the development of ILD in patients with a CTD. In addition, our data suggest that the immunological mechanism involves an ongoing alveolitis, characterized by a delayed type hypersensitivity-like reaction involving NK cells and activated macrophages in the effector phase, on which, at least in scleroderma, D-penicillamine may have a beneficial effect.